Demystifying Medicine Lecture Series

Scientific Discovery and Malaria Interventions for Global Health

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National Institute of Allergy and Infectious Diseases
Bethesda, MD

The Millennium Development Goals (MDGs)

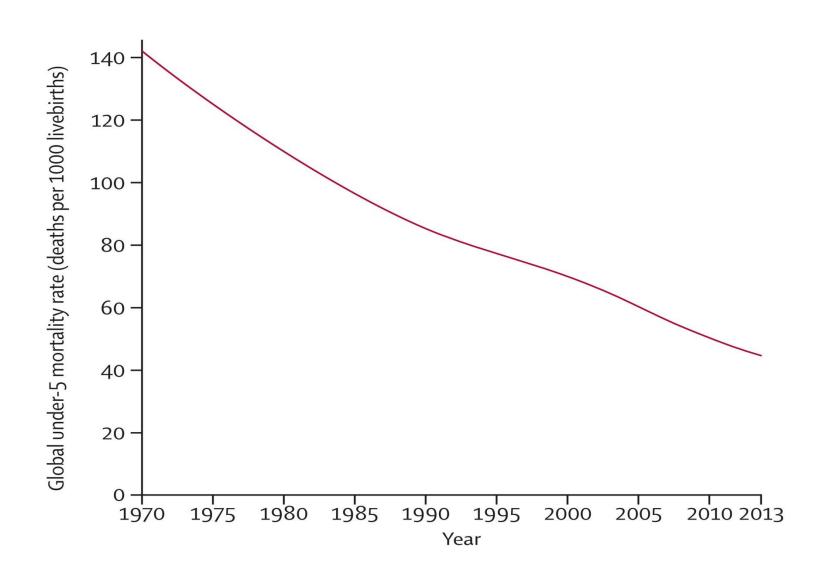
At the United Nations Millennium Summit in September 2000, world leaders committed to work together to mobilize the energy and capacity of the international community, to meet a series of targets to reduce poverty and inequality and named these the Millennium Development Goals (MDGs). The goals are to:

- 1. Eradicate extreme poverty and hunger
- 2. Achieve universal primary education
- 3. Promote gender equality and empower women
- 4. Reduce child mortality
- 5. Improve maternal health
- 6. Combat HIV/AIDS, malaria, and other diseases
- 7. Ensure environmental sustainability
- 8. Develop a global partnership for development



These goals are linked to measurable targets, such as cutting in half the proportion of people living in extreme poverty, halving the proportion of people without access to safe drinking water, and reducing by two thirds the mortality rate of children under five - all by 2015.

Global Under-5 Mortality Rate, 1970-2013

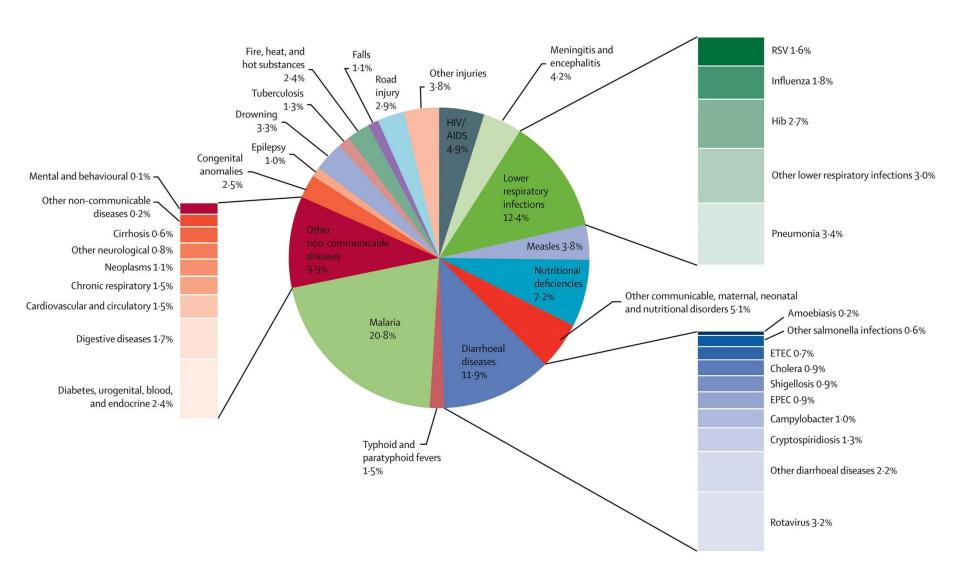


Contributions to Change in Under-5 Deaths, 1990 vs. 2013

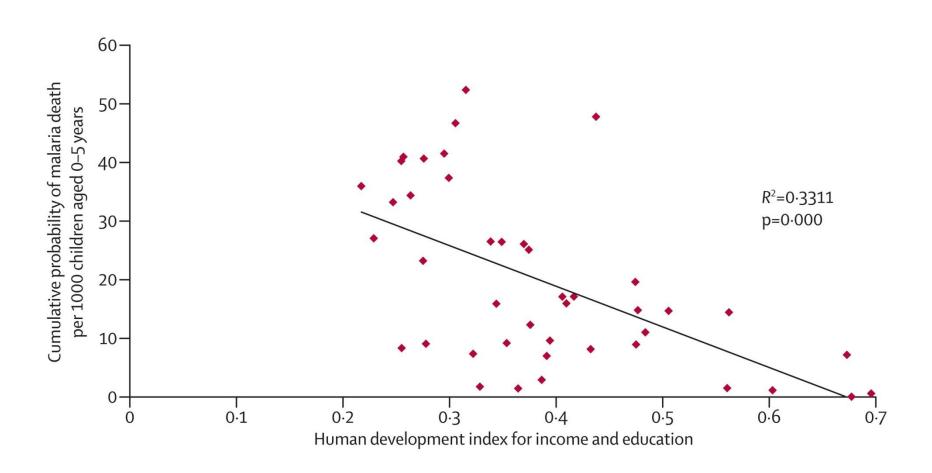
Factor	Change in Deaths (thousands)	Contribution
Fertility	1,424	+24.6%
Maternal education	-2,224	-38.5%
Income	-902	-15.6%
Secular trend*	-4170	-72.1%
Unexplained	+58	+1.0%
HIV/AIDS	+32	+0.6%
TOTAL	-5782	

^{*} Secular trend includes: development assistance for health initiatives, health care system and public health policy improvements, new technologies (vaccines, drugs, ITNs, diagnostics)

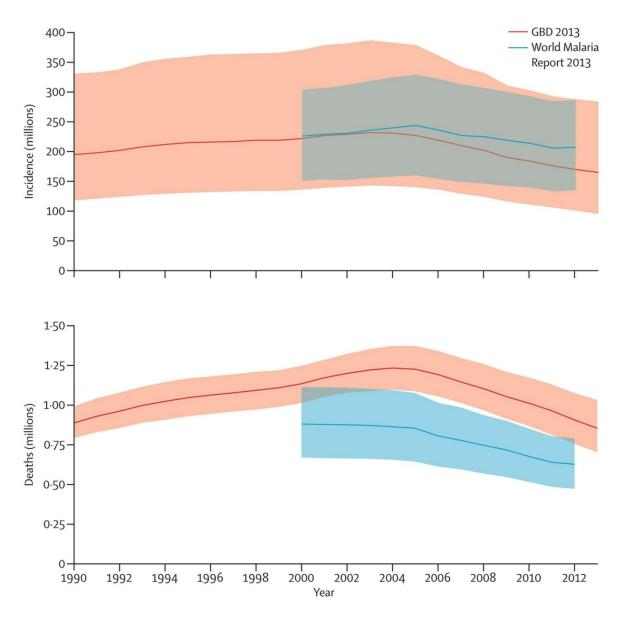
Global Causes of Deaths in 1-4 y/o Children (2010)



Malaria Deaths and Human Development Index in Africa

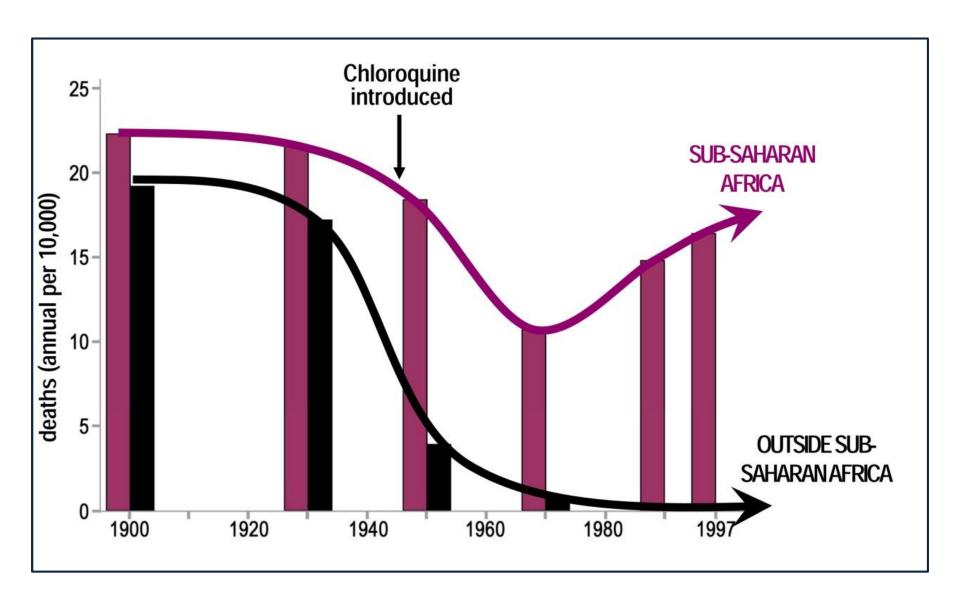


Global Malaria Incidence and Deaths, 1990-2013

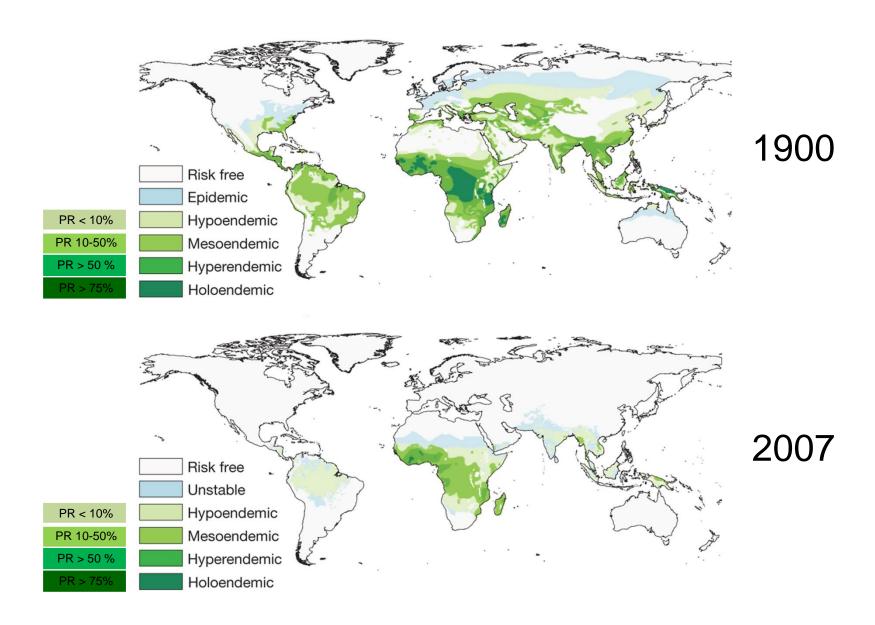


Murry et al. (2014) Lancet PMID: 25059949

Malaria Death Rates in the 20th Century



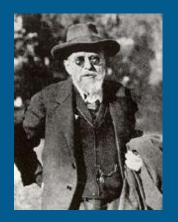
Changes in Malaria Endemicity between 1900 and 2007



Malaria Transmission by Anopheles



Ronald Ross (1857-1932)



Battista Grassi (1854-1925)



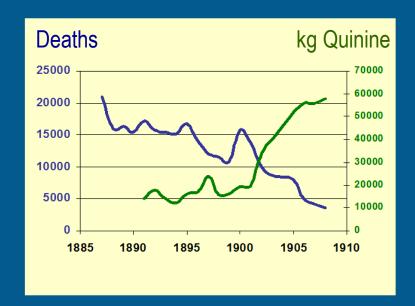
Low, Sambon, & Terzi in the Roman Campagna, 1900



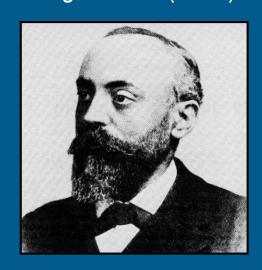
Attacking Malaria Deaths in Italy



"Alms for the poor, struck down in the Campagna. 1694." (Photograph by M. Grizzard (2011) *Clin.Infect.Dis.* May 15, 2012



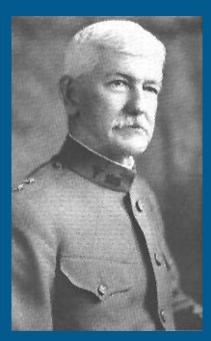
"Unum facere et alterum non omittere" Angelo Celli (1906)



Success in the Panama Canal



Ancon in the Culebra Cut, 1914



William C. Gorgas (1854-1920)

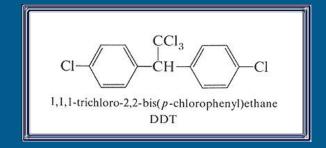
- Mosquito control and quinine distribution program (40,000 doses/day)
- Reduction of malaria incidence from 800/1000 (1906) to 16/1000 (1916)
- Control of yellow fever

Impact of the 1955-1969 Malaria Eradication Campaign

"For the first time it is economically feasible for nations ... to banish malaria completely from their borders."

(P.F. Russell, Man's Mastery of Malaria, 1955)

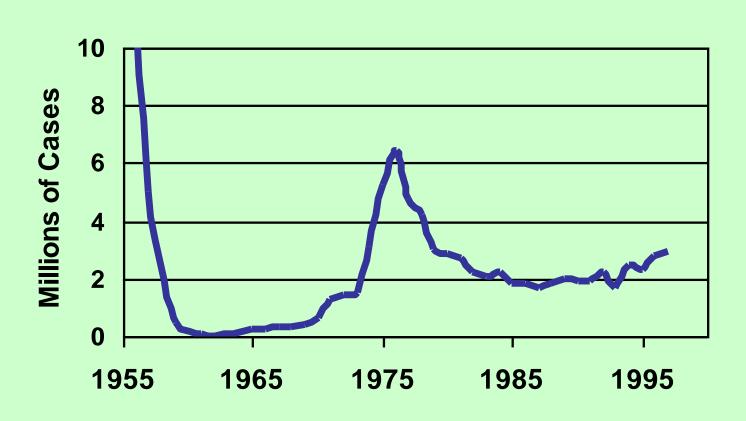






Breakdown of the GMEP and Resurgent Malaria

Malaria Incidence in India



The Route to Chloroquine

A SURVEY OF ANTIMALARIAL DRUGS

1941-1945

8

SUBSIDIZED BY THE OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT ON RECOMMENDATION BY THE COMMITTEE ON MEDICAL RESEARCH

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THE SURVEY STAFF

AND OTHER
CHEMISTS, PHARMACOLOGISTS, AND CLINICIANS WHO
CO-OPERATED IN SUPPLYING THE DATA

In Two Volumes

VOLUME I

Quinine and pre-chloroquine synthetic drugs

Quinine

HO OCH₃

Methylene blue, 1891 (Paul Ehrlich)

Pamaquine, 1926

OCH₃

C₂H₅

OCH₃

C₂H₅

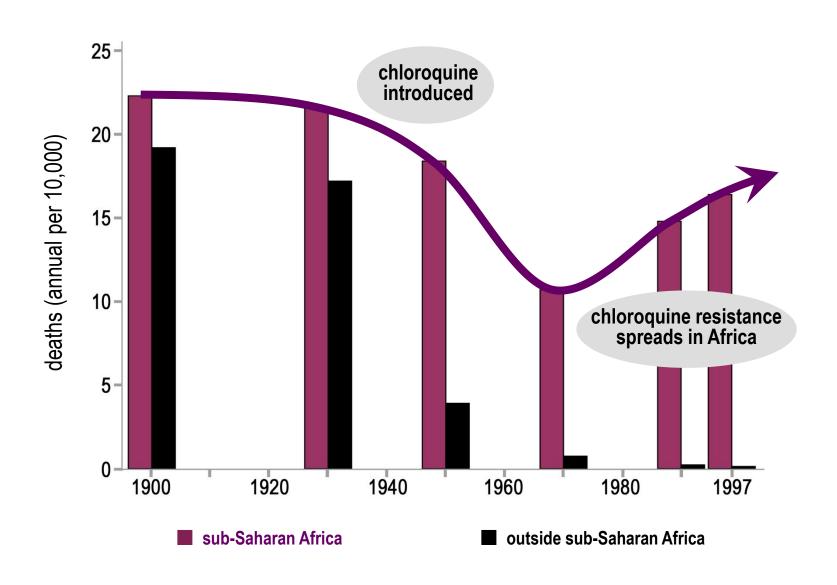
OCH₃

Mepacrine, 1931 (atebrin; quinacrine)

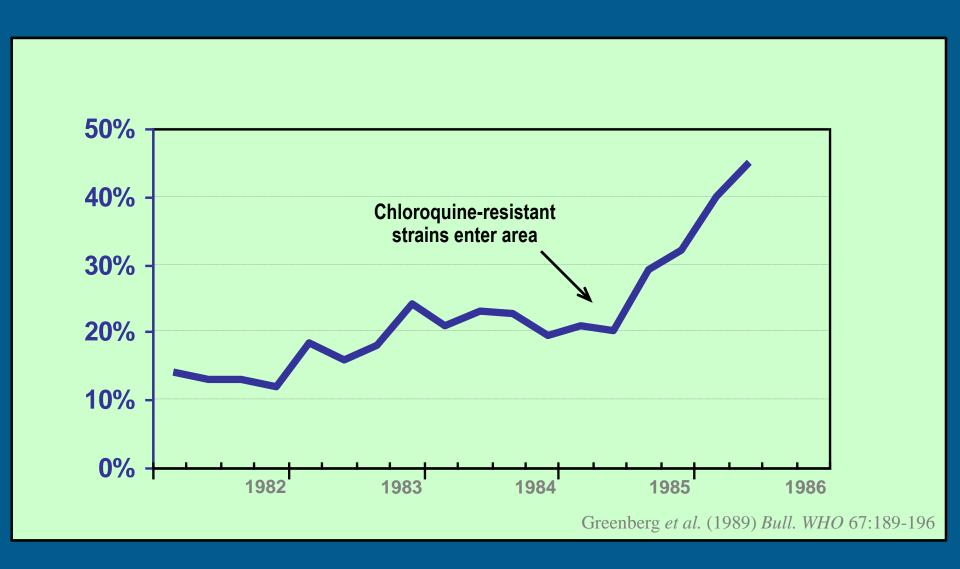
• Chloroquine named antimalarial-of-choice (1945)

Chloroquine, 1936 (Resochin; SN-7618)

Malaria Death Rates in the 20th Century



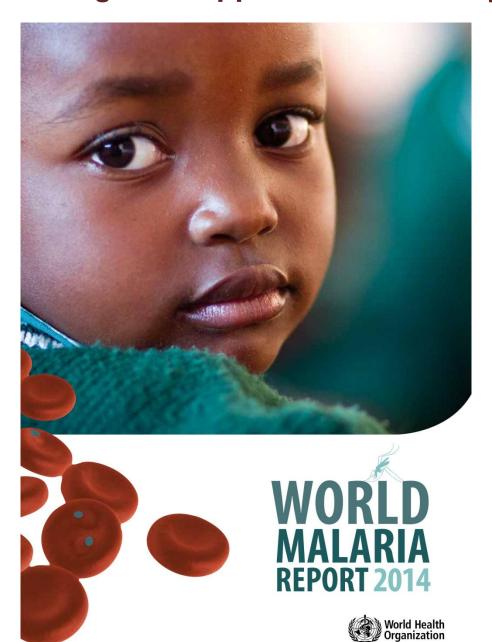
Percentage Pediatric Deaths from Malaria, Mama Yemo Hospital



Malaria Programs and Strategies 1955-2025

1955	8 th World Health Assembly adopts Global Malaria Eradication Program, "vertical" strategy with heavy reliance on DDT spraying for aggressive mosquito control. Program ended in 1969 (WHA resolution 22.39).
1978	31st World Health Assembly adopts a redefined control strategy based on measures adapted to local epidemiological conditions and resources available ("stratification").
1992	Revised Global Malaria Control Strategy endorsed by Health Ministers in Amsterdam. Emphasizes <i>disease</i> control based on decentralized, tailored use of anti-transmission measures and antimalarial treatments; capacity and infrastructure strengthening; political commitment; community partnership.
1998	WHO, UNICEF, UNDP and World Bank establish the Roll Back Malaria (RBM) partnership to scale-up resources and coverage by key interventions.
2008	Malaria Eradication Research Agenda (malERA) convened following Gates Foundation Malaria Forum. RBM releases Global Malaria Action Plan.
2014	WHO Global Malaria Program (GMP) is developing a Global Technical Strategy for 2016-2025, to be the foundation for RBM Global Malaria Action Plan 2.

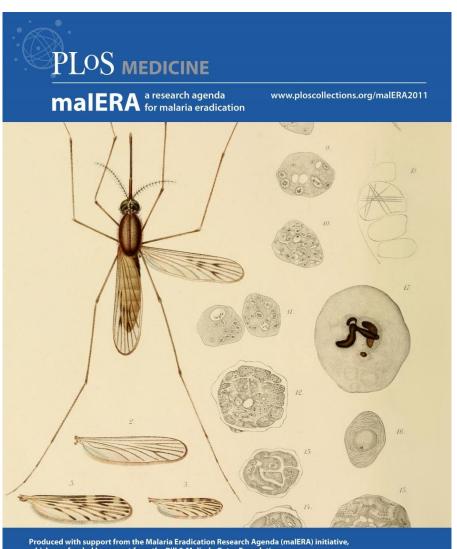
Integrated Approaches of Today's Malaria Control Programs



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The MalERA Initiative (2011 PLoS Collection)



which was funded by a grant from the Bill & Melinda Gates Foundation.

The PLoS Medicine editors have sole editorial responsibility for the content of this collection. Image: Grassi, B. Studi di uno zoologo sulla malaria (1901), courtesy of the Biodiversity Heritage Library.



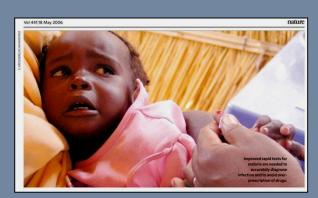
Effective Malaria Programs Requires Multiple Tools (Interface of Molecular Parasitology and Global Health)



Mosquito Transmission Control



Effective Treatments Everywhere

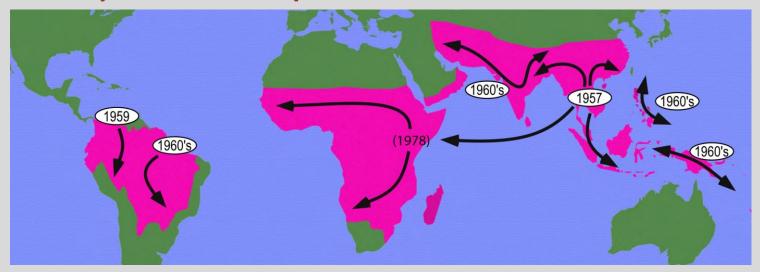


Rapid Diagnostic Tests



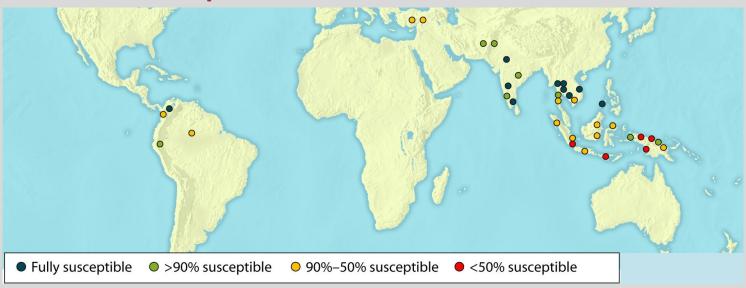
Malaria Vaccines

P. Falciparum Chloroquine Resistance



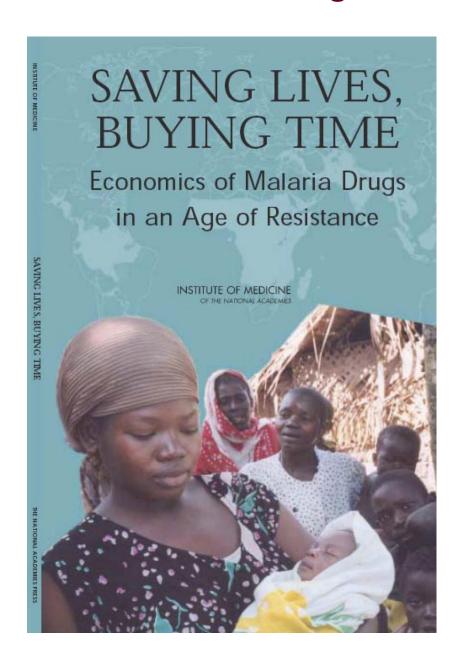
Wellems et al. (2009) J.Clin.Invest. 119: 2496-2505

P. vivax Chloroquine Resistance



Baird (2009) Clin. Microbiol. Rev. 22: 508-534

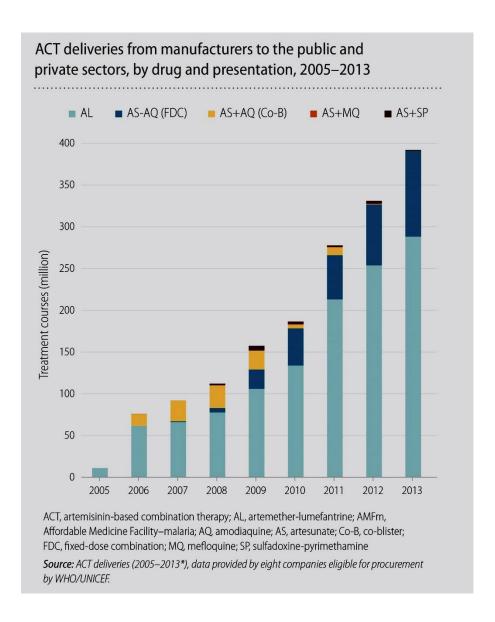
Antimalarial Drugs: Quality, Affordability, Access

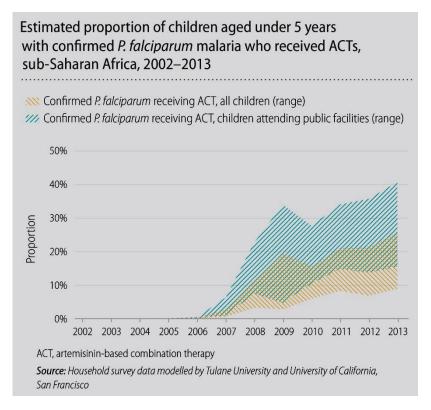


Institute of Medicine Report 2004 recommendation:

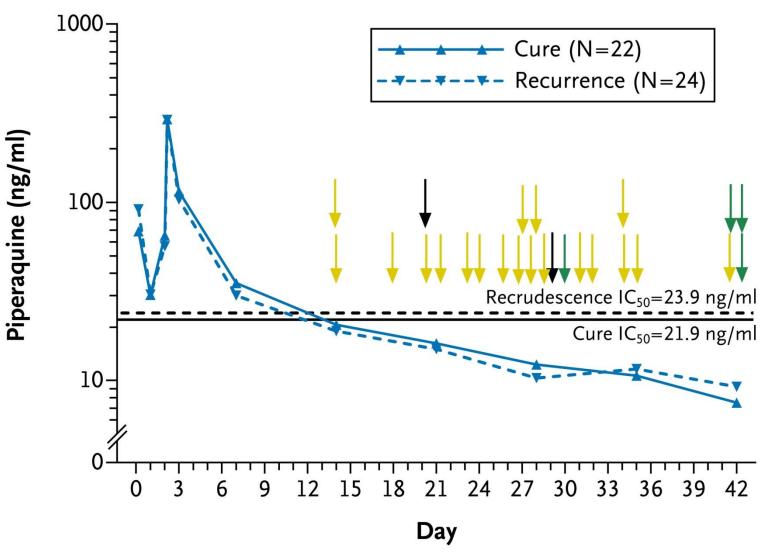
a sustained global subsidy of artemisinins coformulated with other antimalarial drugs (ACTs)

Increasing Use of ACTs for Malaria Treatment



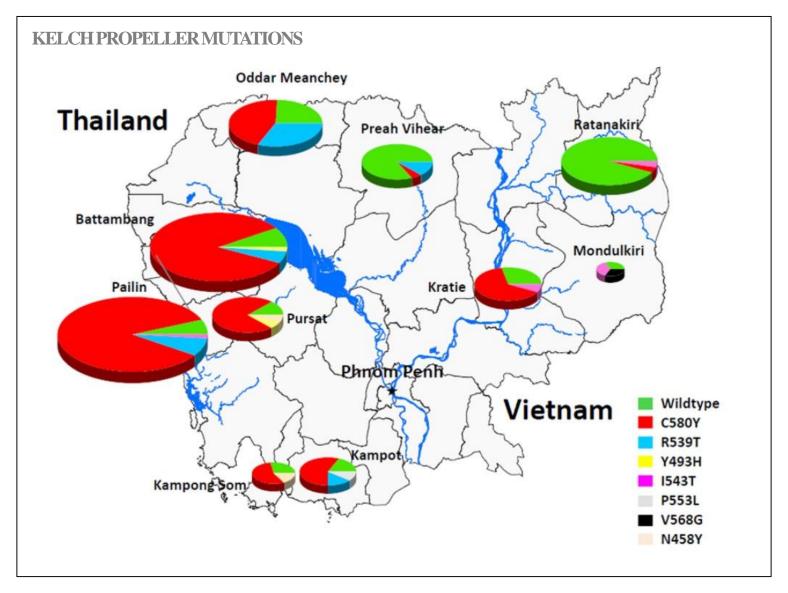


Dihydroartemisinin-Piperaquine Failure in Cambodia



Saunders et al. (2014) N.Engl.J.Med. 371: 484-5

Marker of Delayed Clearance after Artemisinin Treatment in SE Asia



FINANCIAL TIMES

FRIDAY SEPTEMBER 16 2005

Business Life

PUBLIC-PRIVATE PARTNERSHIPS

An antidote to neglected diseases

Alliances of drugmakers, governments and charities are reviving research into overlooked health problems, writes Andrew Jack

'Public-private partnerships work. They are cheap, effective and the best outcome for public health'

HOW PUBLIC-PRIVATE PHARMACEUTICALS PARTNERSHIPS WORK

Public-private partnerships are a promising new way to develop drugs for the "neglected diseases" of the developing world, where the commercial market is usually too small to attract pharmaceutical companies.

The approach of those large companies that are still working in this sector is normally conducted on a "no profit, no loss" basis, and few companies that have withdrawn from the area would be willing to return, even with considerable extra governmental incentives.

Against this background, public-private partnerships have advantages, as well as their own hurdles to overcome.

- Expertise. PPPs using employees and advisers with both industry and non-profit backgrounds can help provide funding, focus and assistance in clinical trials in developing countries, and subsequent registration and distribution.
- Collaboration. Ot her pharmaceutical companies may be willing to share expertise or compounds through PPPs, which they would not offer to direct competitors.
- Agility. Smaller companies may have sufficiently low overheads, or a desire to market one or two late-stage products, to produce neglected disease drugs commercially.
- Challenges. PPPs' main weakness is that they are under-funded, and still largely supported by charitable organisations, while governments have focused on alternative inappropriate incentives and provided little money to date.
- Future incentives. The work of PPPs could be further boosted through co-operating to cut costs, a reduction in patent fees, start-up funding, a prize for companies carrying out the neglected disease research and international donations to help countries purchase and distribute such drugs once developed.

MMV Supported Projects, 4Q 2014

Translational Research Lead **Patient Patient** Human optimisation **Preclinical** volunteers exploratory P218 DHFR Miniportfolio 1 Project OZ439/PQP **BIOTEC** DSM265 **Tafenoquine** Novartis Novartis (Monash/ NIH/Takeda Sanofi GSK LSHTM) SJ733 **DHA- Piperaquine** OZ439/FQ Miniportfolio 3 Projects MMV048 St Jude **Paediatric** Sanofi GSK **GSK** UCT/TIA (Rutgers/NIH) Sigma-Tau Orthologue Leads MMV121 **KAE609** Miniportfolio Sanofi **Novartis** (Dundee) AstraZeneca Oxaboroles PA92 **KAF156** Heterocycles Anacor **Novartis** (Drexel/UW/GNF) Celgene MMV253 Tetraoxanes Heterocycles LSTM/Liverpool (AstraZeneca) Campinas DHODH **GSK030** Screening **GSK** UTSW/UW/Monash Daiichi-Sankyo Aminopyridines Screening UCT Takeda Open Source Screening Drug Discovery Included in MMV portfolio post approval Sydney Eisai 1 Brand name: Coartem® Dispersible Amino-alcohols Pathogen Box 2 Brand name: Artesun® Merck Serono MMV 3 Brand name: Eurartesim® 4 Brand name: Pvramax® 5 Brand names: Coarsucam™, ASAQ/Winthrop®

Other Projects 15 Projects

Development confirmatory Under review * Rectal Artesunate CIPLA/Strides/TDR Pyronaridine-Artesunate **Paediatric** Shin Poong/Iowa * First review or approval by WHO Prequalification, or by regulatory bodies who are ICH members or observers

Access **Post Approval**

Artemether-Lumefantrine Dispersible Novartis

Artesunate for injection Guilin

DHA-**Piperaquine** Sigma-Tau

Pyronaridine-Artesunate Shin Poong

Artesunate Amodiaquine Sanofi/DNDi

Artesunate-Mefloquine CIPLA/DNDi

Sulfadoxine Pyrimethamine+ Amodiaquine Guilin



William Trager, 1910-2005



STUDIES ON CONDITIONS AFFECTING THE SURVIVAL IN VITRO OF A MALARIAL PARASITE (PLASMODIUM LOPHURAE)

BY WILLIAM TRAGER, PH.D.

(From the Department of Animal and Plant Pathology of The Rockefeller Institute for Medical Research, Princeton, New Jersey)

J. Exp. Med. (1941) 74:441-462



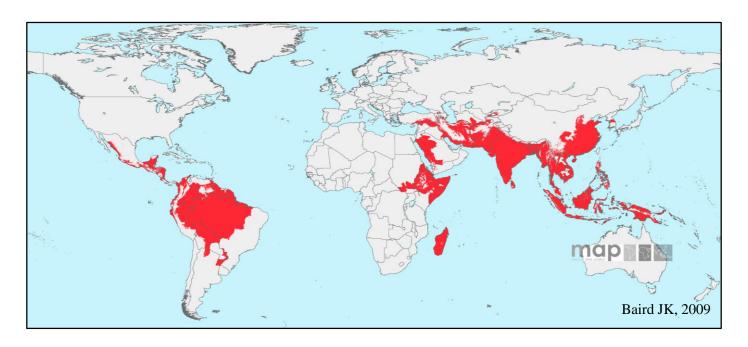
HUMAN MALARIA PARASITES IN CONTINUOUS CULTURE

W Trager and JB Jensen

Science (1976) 193: 673-675

"The impact of continuous cultivation of *P. falciparum* was phenomenal. It spawned a renaissance of research on the immunology, cell biology and molecular biology of this parasite."

P. vivax Burden: 70 – 390 million Cases Annually



"You can't study something you can't grow" (W. Trager)

- P. vivax is a pathogen of major global impact
- Drug screening and vaccine discovery depend upon nonhuman primate and human infections for parasite material
- Until *in vitro* cultivation is solved, molecular and genetic progress on *P. vivax* will be slow and limited

Fake Medicines and **Malaria**



Each year approximately 627,000 people die from malaria (uncertainty



Most cases and deaths occur in Africa



Children under 5 years are the most affected: Every minute 1 child dies of malaria



MALARIA IS A DISEASE THAT CAN BE PREVENTED AND TREATED ... WHEN USING THE RIGHT MEDICINES





WHO recommends treatment with quality-assured





50 countries are on track to reduce their malaria.





Let's keep fake medicines from undermining

1/3 In sub-Saharan Africa - where the burden of OF ANTIMALARIALS IN AFRICA ARE FAKE 10% In Ghana and Cameroon: In Nigeria: up to 40% are fake

children every day. Every 5 minutes a child dies of malaria because of taking fake medicines

medicines contribute to nearly 450,000 preventable deaths every year

FAKE ANTIMALARIAL MEDICINES KILL

FAKE ANTIMALARIALS

- result directly in deaths and morbidity^s
- → increase the incidence of adverse effects[®]
- diminish patients' and health practitioners'
- increase the risk of the emergence and spread

CASE STUDIES



In 2005, a 23 year old man died in Eastern Myanmar from cerebral malaria after being given fake medicine, bought in good faith by his local hospital. When the village committee discovered the cause of this needless death, they were sufficiently angry to collect all packs of these fake antimalarials they could find in local shops and burnt them in front of the whole village.



in 2009, Nigeria intercepted a consignment of nearly 700,000 doses of fake antimalarials. This quantity of fake medicines, if not intercepted, would have been sufficient to give ineffective or dangerous "medications" to hundreds of thousands of pregnant women and children.



In 2012, in Angola, 1,4 million packets of take malaria medicines were found in a container from China, hidden inside a shipment of loudspeakers. The fake pills contained no active ingredient. Instead, they were made of calcium phosphates, fatty acids and yellow pigment. The fakes -- enough to treat more than half the country's annual malaria cases, had they been genuine - are part of a proliferation of bogus malaria drugs in Africa that threaten to undermine years of progress in tackling the disease. A large international investigation is now underway.

RECOMMENDATIONS

- Closely examine the appearance of

- before taking an

- Speak with your doctor or pharmacist if you have

Malaria Rapid Diagnostic Tests









SEARCH

Home

What is an RDT?

Purchasing and Using RDTs

RDT Field Trials

RDT Evaluation Programme

Publications and documents

Joint Workplan

Useful links

Contacts

Making Rapid Diagnosis Work.....

Malaria Rapid Diagnostic Tests (RDTs) assist in the diagnosis of malaria by detecting evidence of malaria parasites in human blood.

This site aims to:



Provide information and guidance for malaria RDTs to malaria control programmes and health services, organizations and individuals considering the use of malaria RDTs.

Provide guidance on evaluation of malaria RDTs. Provide information to manufacturers and users on WHO-FIND Malaria RDT Evaluation Programme.

How To Use a Rapid Diagnostic Test (RDT)



A guide for training at a village and clinic level









<u>Tremendously Expanded RDT use:</u>

"The number of RDTs distributed by national malaria control programmes in the public sector has increased from less than 200,000 in 2005 to more than 108 million in 2012. Manufacturers surveyed by WHO for the World Malaria Report 2013 reported a total of 205 million RDT sales in 2012. Data received from countries reveal that most RDTs (78%) were used in the WHO African Region, followed by the South-East Asia Region (16%)." http://www.who.int/malaria/areas/diagnosis/rapid_diagnostic_tests/en/

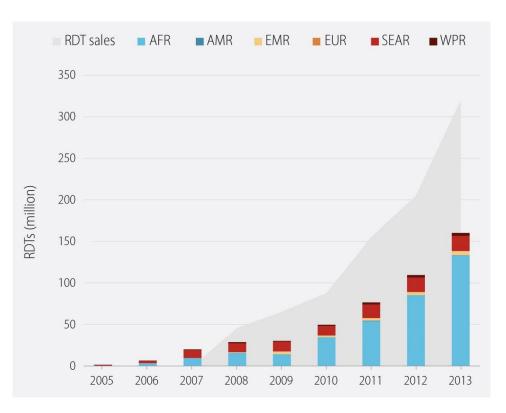
Vol 441|18 May 2006 nature



Neglected tests for neglected patients

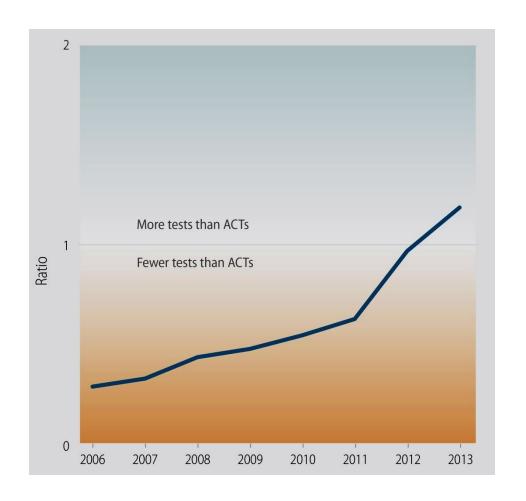


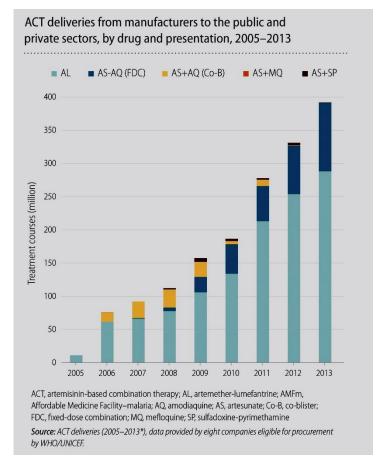
Wellems & Howard (1986) Patent US5130416 A; Shiff, Premji and Minjas (1993) *TRSTMH* **87**: 646-648



World Malaria Report (2014)

Malaria Diagnostic Tests/Distributed ACTs, Africa 2006-2013





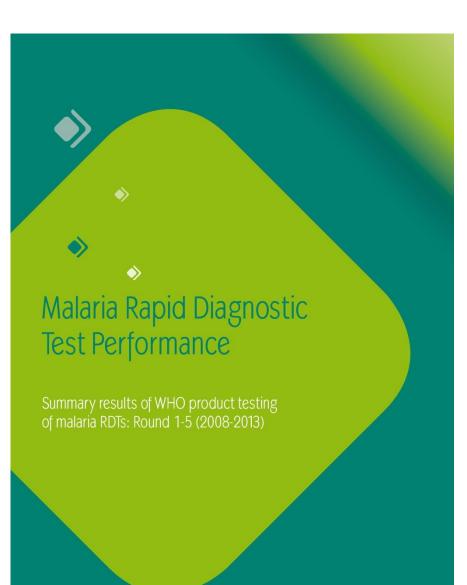
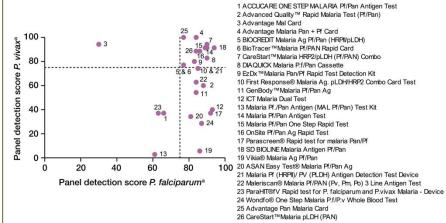






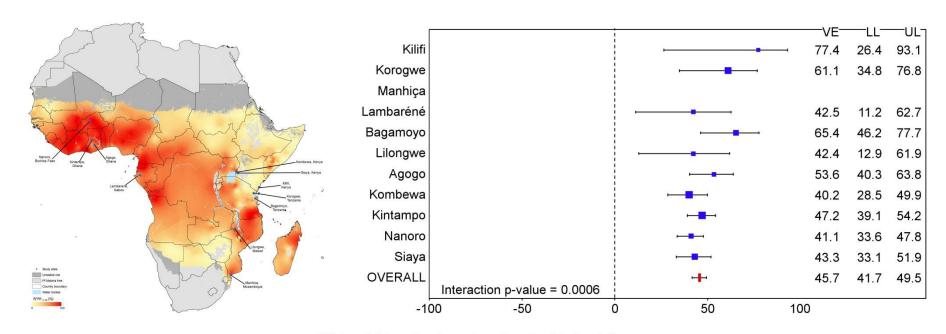


Figure S3: Panel detection score of malaria combination RDTs, meeting WHO procurement criteria for false-positive and invalid rates, in phase 2 of rounds 2–5 against wild-type (clinical) samples containing *P. falciparum* and *P. vivax* at low (200) parasite density (parasites/µL)

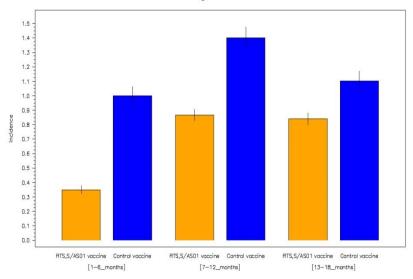


^a Panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at the minimum specified reading time, are positive.

2014: GSK Applies for RTS,S/AS01 Vaccine Regulatory Approval



Children 5-17 months of age at enrollment - clinical malaria



The RTS,S Clinical Trials Partnership (2014) PLoS Med. 7: e1001685

From X-irradiated Sporozoites to the CSP Vaccine (1967-2014)



Ruth Nussenzweig

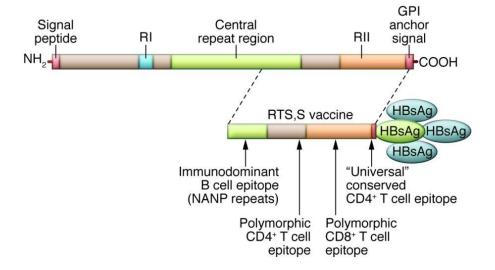
letters to nature

Nature 216, 160 - 162 (14 October 1967); doi:10.1038/216160a0

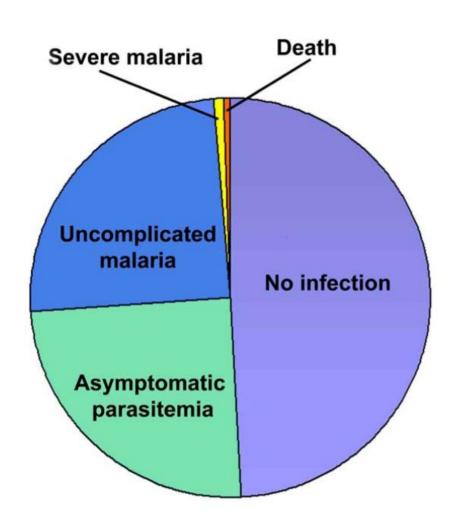
Protective Immunity produced by the Injection of X-irradiated Sporozoites of *Plasmodium berghei*

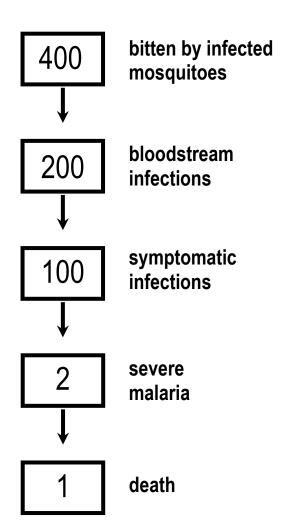
R. S. NUSSENZWEIG, J. VANDERBERG, H. MOST & C. ORTON

Department of Preventive Medicine and Department of Radiology, New York University School of Medicine.



Risk of Infection, Malaria and Death from *P. falciparum* in African Children







ACCELERATING MALARIA VACCINE DEVELOPMENT

About us

Malaria vaccines

Research and development

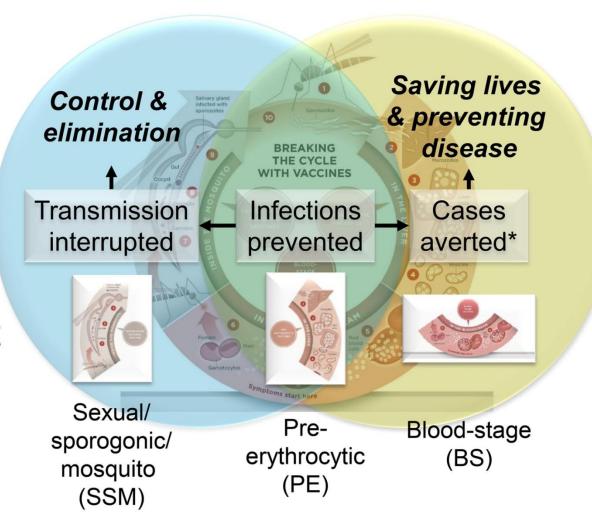
Preparing for vaccines

Publications and resources

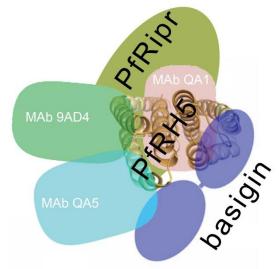
Goal/impact

Outcome

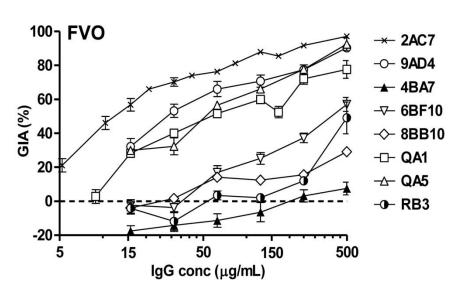
Vaccine target



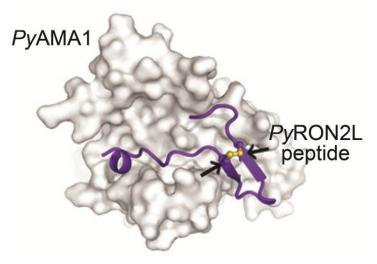
Attacking the Complexes Critical to Erythrocyte Invasion



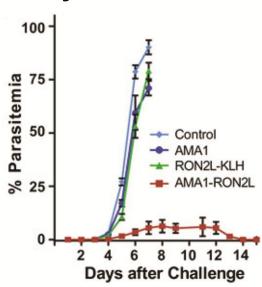
Basigin-PfRH5-PfRipr



Douglas *et al.* (2014) *J.Immunol.* **192:** 245-258; Wright *et al.* (2014) *Nature* doi 0.1038/nature13715; Chen *et al.* (2011) *PLoS Pathogens* **7:** e1002199

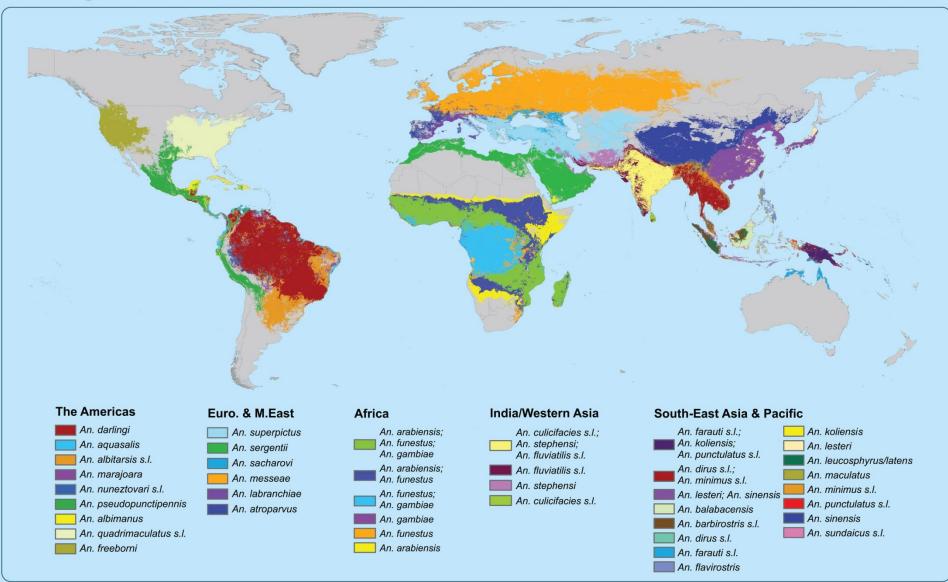


PfAMA1-RON2



Srinivasan et al. (2014) 111: 10311-10316

A global map of dominant malaria vector species



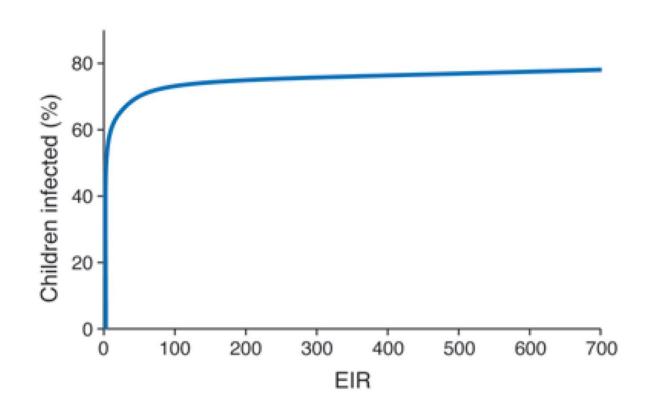






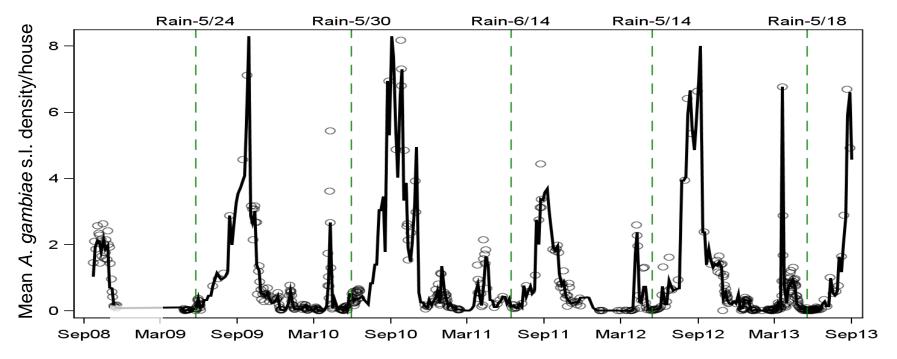


Annual Mosquito Entomological Inoculation Rate (EIR) and Proportion of Individuals Infected with *P. falciparum*



- decreasing EIR from 200 to 100 reduces infection prevalence by 4%
- decreasing EIR from 100 to 1 reduces infection prevalence from 70% to 30%

Wet-Dry Season Ecology of Malaria Mosquitoes





Wet Season (June – October)



Dry Season (November-May)

P. falciparum Can Suppress Midgut Nitration and Evade Mosquito Immunity



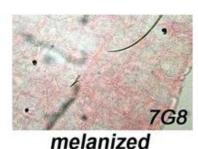
Carolina Barillas-Mury

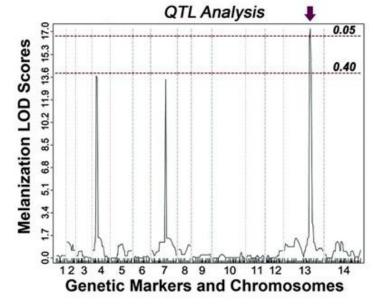
Science 24 May 2013: Vol. 340 no. 6135 pp. 984-987 DOI: 10.1126/science.1235264

The Human Malaria Parasite *Pfs47* Gene Mediates Evasion of the Mosquito Immune System

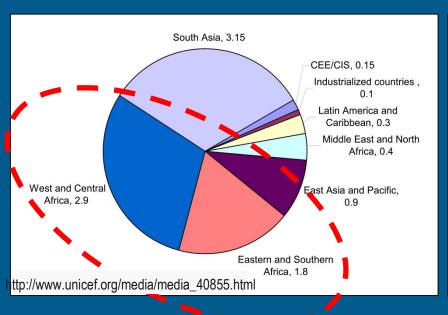
Alvaro Molina-Cruz¹, Lindsey S. Garver¹, Amy Alabaster¹, Lois Bangiolo¹, Ashley Haile¹, Jared Winikor¹, Corrie Ortega¹, Ben C. L. van Schaijk², Robert W. Sauerwein², Emma Taylor-Salmon¹, Carolina Barillas-Mury^{1,*}

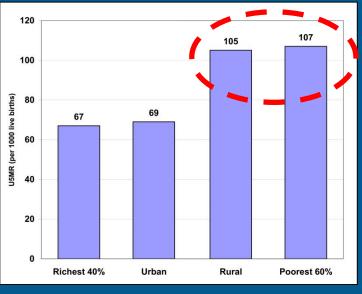






Distribution of Under-Five Child Mortality by Region & Income







"Men and women were sick because they were poor; they became poorer because they were sick and sicker because they were poorer"

Winslow (1951) WHO Monograph Series No. 7



International Bill of Rights





ICESCR commits parties to work toward economic, social, and cultural rights for individuals, including labor rights and the right to health, the right to education, and the right to an adequate standard of living.

(1966)

Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis

Lucy S Tusting, Barbara Willey, Henry Lucas, John Thompson, Hmooda T Kafy, Richard Smith, Steve W Lindsay

Summary

Background Future progress in tackling malaria mortality will probably be hampered by the development of resistance to drugs and insecticides and by the contraction of aid budgets. Historically, control was often achieved without malaria-specific interventions. Our aim was to assess whether socioeconomic development can contribute to malaria control.

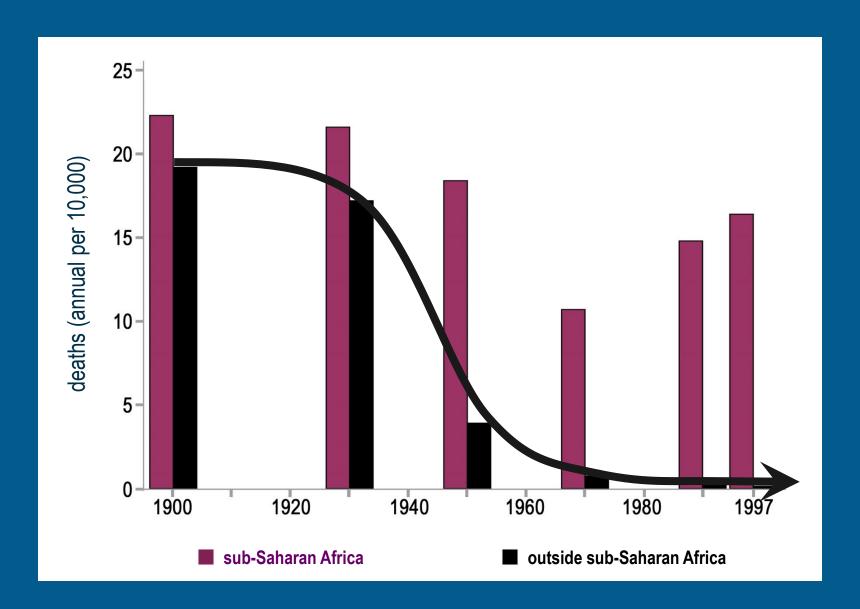
Methods We did a systematic review and meta-analysis to assess whether the risk of malaria in children aged 0–15 years is associated with socioeconomic status. We searched Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, the Campbell Library, the Centre for Reviews and Dissemination, Health Systems Evidence, and the Evidence for Policy and Practice Information and Co-ordinating Centre evidence library for studies published in English between Jan 1, 1980, and July 12, 2011, that measured socioeconomic status and parasitologically confirmed malaria or clinical malaria in children. Unadjusted and adjusted effect estimates were combined in fixed-effects and random-effects meta-analyses, with a subgroup analysis for different measures of socioeconomic status. We used funnel plots and Egger's linear regression to test for publication bias.

Findings Of 4696 studies reviewed, 20 met the criteria for inclusion in the qualitative analysis, and 15 of these reported the necessary data for inclusion in the meta-analysis. The odds of malaria infection were higher in the poorest children than in the least poor children (unadjusted odds ratio [OR] 1.66, 95% CI 1.35-2.05, p<0.001, $I^2=68\%$; adjusted OR 2.06, 1.42-2.97, p<0.001, $I^2=63\%$), an effect that was consistent across subgroups.

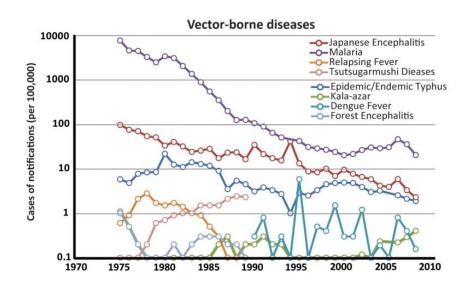
Interpretation Although we would not recommend discontinuation of existing malaria control efforts, we believe that increased investment in interventions to support socioeconomic development is warranted, since such interventions could prove highly effective and sustainable against malaria in the long term.

Funding UK Department for International Development.

Malaria Death Rates in the 20th Century



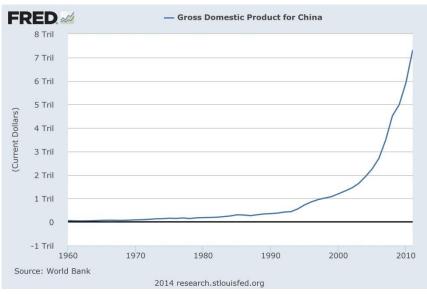
Control of Malaria in PR China



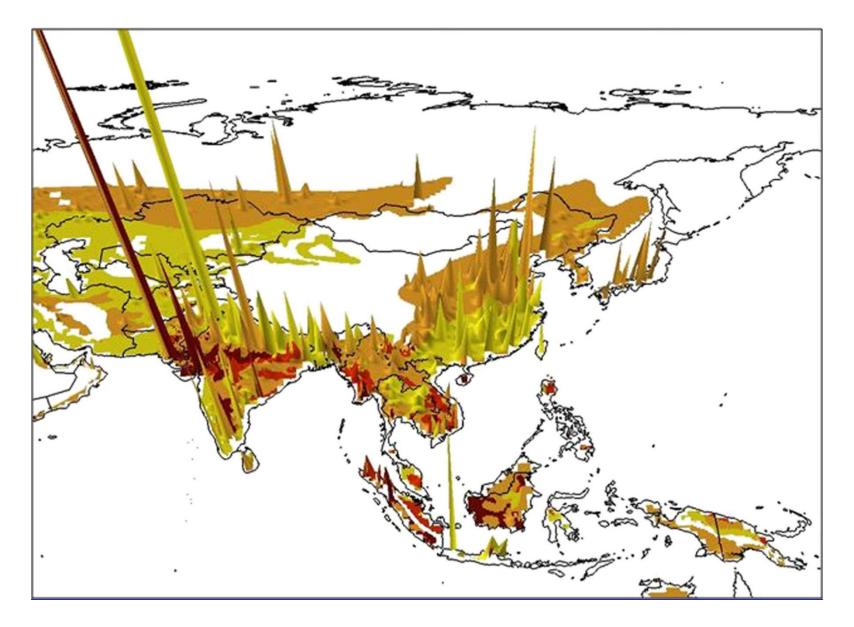


Youyou Tu, winner of the 2011 Lasker-DeBakey Clinical Medical Research Award

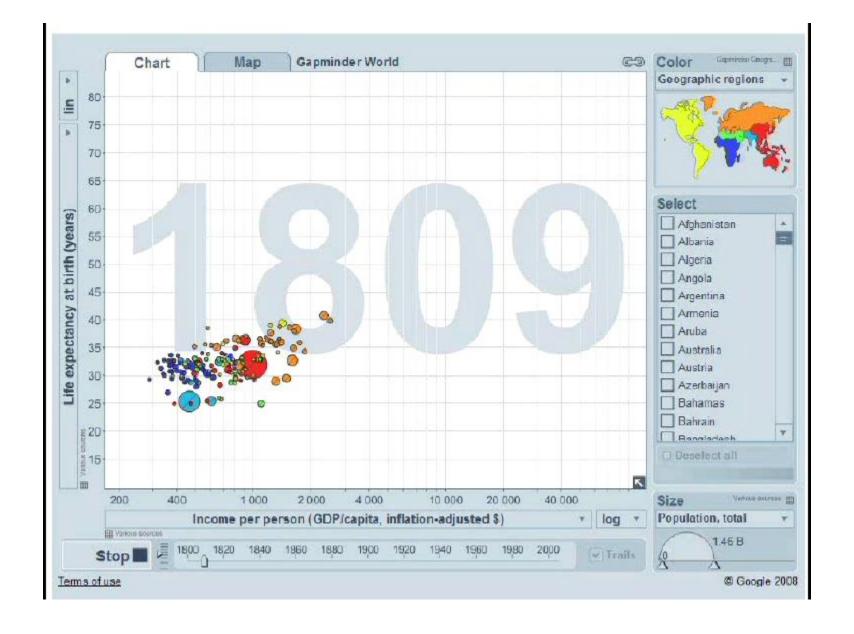
- Primary health care nets
- Community Participation
- Official commitment at all levels
- Integrated antimalarial measures
- Widely available microscopical stations and treatment
- Provincial and regional intersectorial programs
- Scientific research, drug discovery



Urbanization and the Global Decrease of Malaria Transmission



Tatem et al. (2013) Malaria J. 12: 133; Qi et al. (2012) Malaria J. 11: 403



Breaking the Health-Poverty Trap

MAKING MALARIA HISTORY Newsletter

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Report highlights maternal and newborn health

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Leveraging the power of sport to fight malaria

09 July 2014

Malaria pre-elimination in Senegal

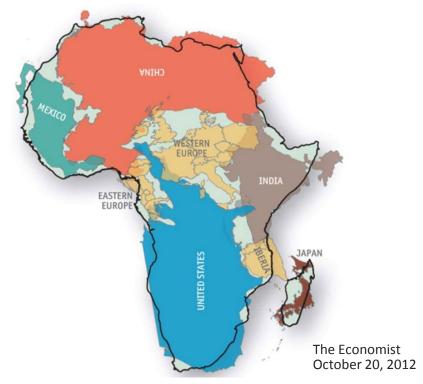
The benefits of investing in malaria



Malaria's impact on child health and broader national economic development is a profound one.

Malaria alone costs the African continent \$12 billion per year and is an economic drain on families, communities, and nations. But current investments are already shrinking the malaria map and improving the health and financial well-being of countries across the African continent. In fact, every \$1 invested in malaria prevention and treatment delivers a return of \$20.



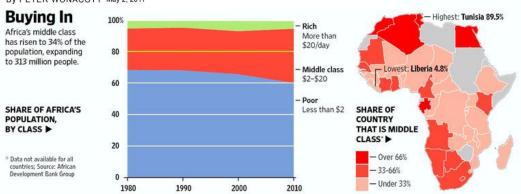


THE WALL STREET JOURNAL = AFRICA RISING

A New Class of Consumers Grows in Africa

Market on Par With China's and India's

By PETER WONACOTT May 2, 2011



THINKPIDGITESS

5 Reasons Why 2013 Was The Best Year In Human History

BY ZACK BEAUCHAMP FOSTED ON DECEMBER 11, 2013 AT 3:34 PM UPDATED: DECEMBER 12, 2013 AT 10:55 AM

Between the brutal civil war in Syria, the government shutdown and all of the deadly dysfunction it represents, the NSA spying revelations, and massive inequality, it'd be easy to for you to enter 2014 thinking the last year has been an awful one.

But you'd be wrong. We have every reason to believe that 2013 was, in fact, the best year on the planet for humankind.

- 1. Fewer people are dying young, and more are living longer.
- 2. Fewer people suffer from extreme poverty, and the world is getting happier.
- 3. War is becoming rarer and less deadly.
- 4. Rates of murder and other violent crimes are in free-fall.
- 5. There's less racism, sexism, and other forms of discrimination.